METABOLOMICS TECHNOLOGY DEVELOPMENT

RELEASE DATE: September 29, 2003

RFA Number: RFA-DK-04-001

Department of Health and Human Services (DHHS)

PARTICIPATING ORGANIZATIONS:

National Institutes of Health (NIH)
(http://www.nih.gov)

This RFA is developed as a roadmap initiative. All NIH Institutes and Centers participate in roadmap initiatives.

CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER(S): 93.847

LETTER OF INTENT RECEIPT DATE: February 24, 2004
APPLICATION RECEIPT DATE: March 24, 2004

THIS RFA CONTAINS THE FOLLOWING INFORMATION

PURPOSE OF THIS RFA

The Institutes and Centers of the National Institutes of Health invite applications for development and application of new technologies in metabolomics to enable research aimed at elucidating biological pathways and networks. The purpose of this initiative is to encourage the development of highly innovative and sensitive tools for identifying and

quantifying cellular metabolites and their fluxes at high anatomical, spatial, and temporal resolution.

The general aim of metabolomics is to identify, measure and interpret the complex time-related concentration, activity and flux of endogenous metabolites in cells, tissues, and other biosamples such as blood, urine, and saliva. For the purposes of this solicitation, metabolites include small molecules that are the products and intermediates of metabolism, but also carbohydrates, peptides, and lipids. The need for innovative technologies for measuring and quantifying metabolites involved in cellular pathways and networks was articulated in the 2003 NIH Roadmapping Initiative. It is expected that the technologies developed under this initiative will play a major role in transferring capabilities to laboratories and research institutes that are investigating the underlying pathways involved in cellular homeostasis, perturbation, development, and aging.

Many ongoing research programs focus on development of new genomics and proteomics tools and utilization of those approaches for studying cellular function. In contrast, relatively few research programs focus on metabolomics technology development and application. This initiative is to encourage the development of highly innovative and sensitive tools for identifying and quantifying cellular metabolites and their fluxes at high anatomical resolution---extending to subcellular--- and at a temporal resolution that would be appropriate to understanding cellular processes at biologically relevant timescales. The scope of projects that would be appropriate ranges from techniques for improving and refining the process of sample separation and processing; to new methods, reagents or instrumentation for identifying and measuring metabolites and their fluxes; to the development and utilization of data reduction, management, and analysis tools needed to establish proof of principle for the technology. New technologies that, if successful, have the potential to be scalable, either as high-throughput applications or as advances that would be used in a large number of laboratories, are especially encouraged. While it is also important to develop data storage, data mining, and pathway modeling capabilities for metabolomics, these issues are explicitly not included in this particular solicitation.

RESEARCH OBJECTIVES

Metabolomics presents unique challenges for sample collection and extraction and for determining analyte identity, concentration, structure, activity and flux in cells. The cellular metabolome is complex, involving several compound classes of small molecules (peptides, lipids, amino acids, carbohydrates) that vary in subunit concentration, size, structure, polarity, and functional groups. Technologies currently in use for metabolomic analysis include NMR, chromatography and mass spectrometry, each of which has significant limitations in quantification, scope, and/or throughput. No one technology can effectively measure, identify and quantify, with sufficient sensitivity and precision, the diverse range of metabolites and their dynamic fluctuations in cells. An integrated set of technologies is needed to address the entire spectrum of challenges for metabolomics. Ideally, new technologies should yield quantitative, comprehensive data and be applicable to achieving anatomical resolution at the cellular and subcellular level.

This initiative seeks to encourage technology developments to address three interrelated components of metabolomics: (1) sample collection, extraction, recovery and validation for specific classes of metabolites; (2) analyte detection, identification, quantification, and structure elucidation; and (3) and data management, reduction and analysis. Specific areas of research emphasis include approaches to address the large dynamic range of metabolite concentration in biological samples, the complexity of metabolite mixtures, the inherent noise of the metabolite profile, the vast number of unidentified compounds present within single samples, and the rapidly changing temporal and spatial variability (flux) of the cell's metabolite complement. It is imperative that new technology incorporate approaches for data management, reduction and analysis to support the technology development. This initiative encourages applications that seek to improve existing technologies, including scaling up to high throughput application, as well as those that seek to develop new approaches that have the potential for measuring entire cellular metabolomes or subsets (e.g., amino acid derivatives, peptide derivatives) whose analysis provides enabling technologies, including appropriate tools for data reduction and analysis. Applications will be evaluated for the potential of the proposed activities to address all three components of metabolomics that are listed above. However, it is anticipated that these components, collectively, might be too broad for a single application to address all three comprehensively. Accordingly, applications may focus on any of the components of metabolomics listed above and may propose single or multiple technologies. Investigators will be expected to clearly define the scope of their activities, and to justify why the specific type(s) of data that the technologies will address are likely to be important to understanding cellular pathways and networks.

This initiative encourages applications involving multi-disciplinary teams representing self-assembled groups of collaborating investigators, at one or several sites, with specific expertise in metabolomics technology as well as data management and statistical approaches relevant to the proposed technology. Partnerships between academia and industry are encouraged, to facilitate technology transfer and capacity building at academic institutions.

This solicitation seeks to encourage highly innovative and potentially risky approaches. However, it is likely that some proposed technologies will be more mature, at the onset, than others. Accordingly, this RFA will use the NIH Phased Innovation (R21/R33) and Exploratory/Development Research Grant Phase 2 (R33) award mechanisms. Applicants may submit a combined R21/R33 application, or a stand-alone R33 application if technological feasibility can be documented at the time of submission. Applicants may request up to three years of funding, either using the R33 mechanism for the entire time, or via a phased format that begins as an R21 award and transitions to an R33 award. The duration of the R21 phase may be either one year or two years. A grant may be considered for renewal or supplementation after the three year period of support if it is obvious that a newly developed technology will have exceptionally high impact on the field, but additional time is required to optimize it. Applicants for a phased award cannot request more than $800,000 in direct costs per year of the R21 phase. Applicants may not

request more than $1.5 million in direct costs per year of the R33 phase, or per year of the entire award if it is solely R33. It is emphasized that the figures above are a maximum. We envisage that a range of activities could be appropriate for this solicitation, from an individual well-focused goal, to a set of closely related or well-integrated technology development aims.

The R21 award mechanism supports innovative, high-risk/high-impact research requiring preliminary testing or development; exploration of the use of approaches and concepts new to a specific substantive area; or research and development of new technologies, techniques, or methods. Applications will be considered high-impact if they demonstrate the potential for ground-breaking significance, and high-risk because they either lack sufficient preliminary data to ensure their feasibility, or propose use of a new model or a unique system.

Eligibility for transition to the R33 phase will be based on successful completion of the negotiated milestones, which must be specified in the application, and programmatic review. The objective of the R33 phase is continuation of innovative exploratory and developmental research initiated during the R21 mechanism. Research conducted in the R33 phase will focus on demonstrating proof of principle for application of the technology to elucidate functional components and interactions of metabolites within biological pathways and networks. While the intent of the R21 award is to encourage the development of highly innovative technologies, the potential for the proposed technology to advance our understanding of biological pathways and networks will be an important criterion for evaluating the R33 phase of an application or the entire application, if it is for a stand—alone R33 award. Development of complex, integrated technologies for metabolomics problems will require a context within which methods development can proceed. Accordingly, investigators should select a model system, defined at the cellular or subcellular level, to serve as a framework for demonstrating the technological capabilities of the resource.

MECHANISM OF SUPPORT

This RFA will use the NIH Phased Innovation (R21/R33) and Exploratory/Development Research Grant Phase 2 (R33) award mechanisms. As an applicant you will be solely responsible for planning, directing, and executing the proposed project. This RFA is a one-time solicitation. Future unsolicited, competing-continuation applications based on this project will compete with all investigator-initiated applications and will be reviewed according to the customary peer review procedures. The anticipated award date is September 30, 2004. Applications that are not funded in the competition described in this RFA may be resubmitted as NEW investigator-initiated applications using the standard receipt dates for NEW applications described in the instructions to the PHS 398 application.

This RFA uses just-in-time concepts. It also uses the non-modular budgeting format. Please follow the instructions for non-modular budget research grant applications. This

program does not require cost sharing as defined in the current NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2001/part_i_1.htm.

FUNDS AVAILABLE

The participating ICs intend to commit approximately $7.4 million in FY 2004 to fund 6 to 8 new grants in response to this RFA. An applicant may request a project period of 3 years and a budget for direct costs of up to $800,000 per year for the one or two year R21 phase, and up to $1.5 million per year for the R33 phase or for each year of a stand-alone R33 award. Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size of each award will also vary. Although the financial plans of the ICs provide support for this program, awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications.

ELIGIBLE INSTITUTIONS

You may submit (an) application(s) if your institution has any of the following characteristics:

o For-profit or non-profit organizations
o Public or private institutions, such as universities, colleges, hospitals, and laboratories
o Eligible agencies of the federal government
o Domestic or foreign institutions/organizations

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

SPECIAL REQUIREMENTS

Principal investigators, plus key personnel if appropriate, are expected to participate in an annual meeting of grantees. The purpose of these meetings is to discuss scientific advances; the potential for collaborations, data and technology sharing; and other research opportunities. Funds for travel to the meeting should be requested in the budget.

WHERE TO SEND INQUIRIES

We encourage inquiries concerning this RFA and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into two areas: scientific/research and financial or grants management issues:

o Direct your questions about scientific/research issues to:

Maren R. Laughlin, Ph.D.
Division of Diabetes, Endocrinology and Metabolism
National Institute of Diabetes and Digestive and Kidney Diseases
6707 Democracy Boulevard, Room 6101, MSC 5460
Bethesda, MD 20892-5460
Telephone: (301) 594-8802
FAX: (301) 480-3503
Email: laughlinm@extra.niddk.nih.gov

o Direct your questions about financial or grants management matters to:

Ms. Kathleen Shino
Grants Administration Branch
Division of Extramural Activities
National Institute of Diabetes and Digestive and Kidney Diseases
6707 Democracy Boulevard, Room 708, MSC 5456
Bethesda, MD 20892-5456
Telephone: (301) 594-8869
FAX: (301) 594-9523
Email: shinok@extra.niddk.nih.gov

LETTER OF INTENT

Prospective applicants are asked to submit a letter of intent that includes the following information:

o Descriptive title of the proposed research
o Name, address, and telephone number of the Principal Investigator
o Names of other key personnel
o Participating institutions
o Number and title of this RFA

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows IC staff to estimate the potential review workload and plan the review.

The letter of intent is to be sent by the date listed at the beginning of this document. The letter of intent should be sent to:
Maren R. Laughlin, Ph.D.
Division of Diabetes, Endocrinology and Metabolism
National Institute of Diabetes and Digestive and Kidney Diseases
6707 Democracy Boulevard, Room 6101, MSC 5460
Bethesda, MD 20892-5460

Telephone: (301) 594-8802
FAX: (301) 480-3503
Email: laughlinm@extra.niddk.nih.gov

SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). Applications must have a DUN and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the Universal Identifier when applying for Federal grants or cooperative agreements. The DUNS number can be obtained by calling (866) 705-5711 or through the web site at http://www.dunandbradstreet.com/. The DUNS number should be entered on line 11 of the face page of the PHS 398 form. The PHS 398 document is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

USING THE RFA LABEL: The RFA label available in the PHS 398 (rev. 5/2001) application form must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked. The RFA label is also available at: http://grants.nih.gov/grants/funding/phs398/labels.pdf.

SENDING AN APPLICATION TO THE NIH: Submit a signed, typewritten original of the application, including the Checklist, and five signed photocopies, in one package to:

Center for Scientific Review
National Institutes Of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express/courier service)

APPLICATION PROCESSING: Applications must be received on or before the application receipt date listed in the heading of this RFA. If an application is received after that date, it will be returned to the applicant without review.

Although there is no immediate acknowledgement of the receipt of an application, applicants are generally notified of the review and funding assignment within 8 weeks.

The Center for Scientific Review (CSR) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. However, when a previously unfunded application, originally submitted as an investigator-initiated application, is to be

submitted in response to an RFA, it is to be prepared as a NEW application. That is, the application for the RFA must not include an Introduction describing the changes and improvements made, and the text must not be marked to indicate the changes from the previous unfunded version of the application.

PEER REVIEW PROCESS

Upon receipt, applications will be reviewed for completeness and responsiveness by the NIH). Incomplete and nonresponsive applications will not be reviewed.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group) in accordance with the review criteria stated below. As part of the initial merit review, all applications will:

o Undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed and assigned a priority score

o Receive a written critique

o Receive a second level review by the an appropriate National Advisory Council or Board

REVIEW CRITERIA

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, reviewers will be asked to evaluate the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. The scientific review group will address and consider each of the following criteria in assigning the application's overall score, weighting them as appropriate for each application.

o Significance
o Approach
o Innovation
o Investigator
o Environment

The application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

SIGNIFICANCE: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

APPROACH: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

INNOVATION: Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

INVESTIGATOR: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

ENVIRONMENT: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

ADDITIONAL REVIEW CRITERIA: In addition to the above criteria, the following item will be considered in the determination of scientific merit and the priority score, for applications utilizing the R21/R33 phased innovation mechanism:

Milestones: How appropriate are the proposed milestones against which to evaluate the demonstration of feasibility for transition to the R33 development phase?

PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISK: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed. (See criteria included in the section on Federal Citations, below).

INCLUSION OF WOMEN, MINORITIES AND CHILDREN IN RESEARCH: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated. (See Inclusion Criteria in the sections on Federal Citations, below).

CARE AND USE OF VERTEBRATE ANIMALS IN RESEARCH: If vertebrate animals are to be used in the project, the five items described under Section f of the PHS 398 research grant application instructions (rev. 5/2001) will be assessed.

ADDITIONAL REVIEW CONSIDERATIONS

Sharing Research Data

Applicants requesting more than $500,000 in direct costs in any year of the proposed research must include a data sharing plan in their application. The reasonableness of the data sharing plan or the rationale for not sharing research data will be assessed by the reviewers. However, reviewers will not factor the proposed data sharing plan into the determination of scientific merit or priority score. The NIH policy on data sharing, as well as guidance on this subject, can be found at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html.

BUDGET: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research.

RECEIPT AND REVIEW SCHEDULE

Letter of Intent Receipt Date: February 24, 2004
Application Receipt Date: March 24, 2004
Peer Review Date: June/July 2004
Council Review: September 2004
Earliest Anticipated Start Date: September 30, 2004

AWARD CRITERIA

Award criteria that will be used to make award decisions include:

o Scientific merit (as determined by peer review)
o Availability of funds
o Programmatic priorities

REQUIRED FEDERAL CITATIONS

HUMAN SUBJECTS PROTECTION: Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.
http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm

SHARING RESEARCH DATA: Starting with the October 1, 2003 receipt date, investigators submitting an NIH application seeking more than $500,000 or more in direct costs in any single year are expected to include a plan for data sharing or state why this is not possible. http://grants.nih.gov/grants/policy/data_sharing Investigators should seek guidance from their institutions, on issues related to institutional policies, local IRB rules, as well as local, state and Federal laws and regulations, including the Privacy Rule.

Reviewers will consider the data sharing plan but will not factor the plan into the determination of the scientific merit or the priority score.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS: The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects that is available at http://grants.nih.gov/grants/funding/children/children.htm

REQUIRED EDUCATION ON THE PROTECTION OF HUMAN SUBJECT PARTICIPANTS: NIH policy requires education on the protection of human subject participants for all investigators submitting NIH proposals for research involving human subjects. You will find this policy announcement in the NIH Guide for Grants and Contracts Announcement, dated June 5, 2000, at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

HUMAN EMBRYONIC STEM CELLS (hESC): Criteria for federal funding of research on hESCs can be found at http://stemcells.nih.gov/index.asp and at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html. Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (see http://escr.nih.gov). It is the responsibility of the applicant to provide, in the project description and elsewhere in the application as appropriate, the official NIH identifier(s) for the hESC line(s) to be used in the proposed research. Applications that do not provide this information will be returned without review.

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT:
The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm.

Applicants may wish to place data collected under this PA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of

time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

STANDARDS FOR PRIVACY OF INDIVIDUALLY IDENTIFIABLE HEALTH INFORMATION:
(if applicable) The Department of Health and Human Services (DHHS) issued final modification to the "Standards for Privacy of Individually Identifiable Health Information", the "Privacy Rule," on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the DHHS Office for Civil Rights (OCR). Those who must comply with the Privacy Rule (classified under the Rule as "covered entities") must do so by April 14, 2003 (with the exception of small health plans which have an extra year to comply).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR website (http://www.hhs.gov/ocr/) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html.

URLs IN NIH GRANT APPLICATIONS OR APPENDICES: All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

HEALTHY PEOPLE 2010: The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This RFA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople.

AUTHORITY AND REGULATIONS: This program is described in the Catalog of Federal Domestic Assistance at http://www.cfda.gov/ and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284)(cite appropriate authorizations) and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92 (cite relevant regulations). All awards are subject to the terms and conditions, cost

principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm (also cite other relevant policies)

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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Department of Health and Human Services

National Institutes of Health (NIH)
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